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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/719,990	HOWE, ALAN	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-36,38 and 39* is/are pending in the application.

4a) Of the above claim(s) *15-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-14 and 38-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/20/2006 has been entered.

Claims 1-4, 6-36 and 38-39 are currently pending.

Claims 15-36 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 1-4, 6-14 and 38-39 are currently under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 6-9 and 38-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2164).

In the instant case, the claims are drawn to a phosphoprotein detection reagent comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator metal ion moiety, wherein the metal ion is selected from the group consisting of Fe^{3+}, Al^{3+}, Yb^{3+} and Ga^{3+}, and the chelator-metal ion moiety selectively binds to a phosphorylated amino acid residue in a phosphoprotein. Thus, while the claims reasonably conveys the metal ion, the claims encompass a genus of chelators defined solely by its principal biological property, which is simply a wish to know the identity of any material with that biological property.

The specification teaches (page 17, lines 31+) that the term "chelator-metal ion moiety" refers to a polydentate chelator molecule to which a metal ion is coordinated, wherein the polydentate chelator molecule includes, but is not limited to bidentate, tridentate, tetradentate, and pentadentate chelators, and further provides a respresentative number of polydentate chelator moieties. Thus, while the specification reasonably conveys a representative number of polydentate chelators, there is insufficient written description encompassing the genus of chelators because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics are not set forth in the specification as-filed, and therefore, is not commensurate in scope with the claimed invention. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddles v.Baird, 30 USPQ2d 1481, 1483. In Fiddles v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function" and the expression "an antibiotic penicillin" fails to distinguish a particular penicillin molecule from others possessing the same activity and which therefore, fails to satisfy the written description requirement. Similarly, a chelator moiety part of the chelator-metal ion moiety useful for biding selectively to a phosphorylated amino acid residue in a phosphoprotein does not distinguish any particular chelator moiety from others having the same activity or function and as such does not satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

In the absence of structural characteristics that are shared by members of the genus; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 7-8 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Savage et al. (US 6,670,159, 12/31/1997).

Savage et al. teach a chelated metal conjugate comprising a chelator having tridenate chelator function towards multivalent metal ions, wherein said chelate is covalently linked via an amide bond to a molecule having a primary amine group (column 2, lines 24-30). With regards to the chelator, the patent teaches that the chelators include, but are not limited to, nitrilotriacetic acid (abstract). With regards to the molecule, the patent teaches that the molecules include, but are not limited to, enzymes, fluorescent labels, biotin or other detectable moieties (column 2, lines 39-41). With regards to the metal, the patent teaches that the metals include, but are not limited to, iron or nickel, wherein iron activated chelate conjugates allows for detection of phosphate-containing molecules (column 4, lines 50-52 and column 10, Example XI). Moreover, the patent teach a method of synthesizing the chelate conjugate comprising reacting nitrilotrioacetic acid with a detectable moiety to generate a conjugate and mixing the conjugate with a metal ion-containing solution comprising Fe^{3+} (column 4 to column 5, Examples I-II). Thus, while Savage et al. do not explicitly teach that the chelated metal conjugate is soluble in an aqueous medium, the claims are drawn to the product, per se, and inherently, such a chelated metal conjugate would be soluble in an aqueous medium because the claimed conjugate appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Savage et al. (US 6,670,159, 12/31/1997) in view of Zachariou et al. (Journal of Protein Chemistry 1995; 14: 419-430).

Savage et al. teach, as applied to claims 1-3, 7-8 and 10 above, a chelated metal conjugate comprising a chelator having tridenate chelator function towards multivalent metal ions, wherein said chelate is covalently linked via an amide bond to a molecule having a primary amine group (column 2, lines 24-30). With regards to the chelator, the patent teaches that the chelators include, but are not limited to, nitrilotriacetic acid (abstract). With regards to the molecule, the patent teaches that the molecules include, but are not limited to, enzymes, fluorescent labels, biotin or other detectable moieties (column 2, lines 39-41). With regards to the metal, the patent teaches that the metals include, but are not limited to, the most commonly used metals in metal affinity interactions such as iron or nickel, wherein iron activated chelate conjugates allows for detection of phosphate-containing molecules (column 4, lines 50-52 and column 10, Example XI). Moreover, Savage et al. teach that iminodiacetic acid have been used in metal-ion chromatography for the detection of ferric ions (column 1, lines 33-37). Moreover, Savage et al. teach that it is recognized that in metal-ion chromatography the chelating functionality used to immobilize the metal to construct the chelator metal conjugate is important (column 1, lines 33-35). For example, the patent teaches that iminodiacetic acid has been used with iron due to its tight binding characteristics with ferric ions (column 1, lines, 35-37).

Savage et al. do not explicitly teach that the chelator is iminodiacetic acid.

Zachariou et al. teach that IDA is a tridentate metal chelate (page 428, 2nd column, 8th line from bottom). Specifically, the reference teaches the purification of proteins using metal ions bound to IDA, wherein the metal ions include but are not limited to Fe^{3+}.

It would have been *prima facie* obvious to one of skill in the art at the time the invention was made to combine the teachings of the references because each of metal chelates have been individually taught in the prior art to be effective at protein purification. Moreover, one would have been motivated to use iminodiacetic acid as the metal chelate because Zachariou et al. teach that IDA has tridentate functionality. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by substituting IDA which has a high binding affinity for Fe3+ for NTA as taught by Savage et al. in view of Zachariou, one would achieve a metal chelate with high affinity for Fe3+ which can be used for the detection of phosphoproteins.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Savage et al. (US 6,670,159, 12/31/1997) in view of Zhou et al. (J. Am. Soc. Mass Spectrom 2000; 11: 273-282).

Savage et al. teach, as applied to claims 1-3, 7 and 10 above, a chelated metal conjugate comprising a chelator having tridenate chelator function towards multivalent metal ions, wherein said chelate is covalently linked via an amide bond to a molecule having a primary amine group (column 2, lines 24-30). With regards to the chelator, the patent teaches that the chelators include, but are not limited to, nitrilotriacetic acid (abstract). With regards to the molecule, the patent teaches that the molecules include, but are not limited to, enzymes, fluorescent labels, biotin or other detectable moieties (column 2, lines 39-41). With regards to the metal, the patent teaches that the metals include, but are not limited to, the most commonly used metals in metal affinity interactions such as iron or nickel, wherein iron activated chelate conjugates allows for detection of phosphate-containing molecules (column 4, lines 50-52 and column 10, Example XI). Moreover, Savage et al. teach that iminodiacetic acid have been used in metal-ion chromatography for the detection of ferric ions (column 1, lines 33-37).

Savage et al. do not explicitly teach that the metal ion moiety is Ga^{3+}.

Zhou et al. teach the detection of phosphoproteins and peptides using Ga^{3+} bound nitrilotriacetic acid and Fe3+ bound nitrilotriacetic acid (page 275, 1st column, 3rd full paragraph). The reference further teaches that Ga3+ shows less overall suppression effect and the ability to isolated phosphoproteins with multiple phosphate groups, whereas the selectivity for monophosphorylated peptides is better using Fe3+ bound nitrilotriacetic acid (page 274, 2nd column, 1st full paragraph).

It would have been *prima facie* obvious to one of skill in the art at the time the invention was made to combine the teachings of the references so as to optimize the metal ion for a particular phosphoprotein. One would have been motivated to do so because each of the metal ions bound to nitrilotrioacetic acid have been individually taught in the prior art to be effective at detecting phosphorylated proteins. Moreover, in view of Zhou et al., the choice of metal ion can be optimized for the highest selectivity towards monophosphorylated proteins versus proteins having multiple phosphate groups. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by substituting the metal ion as taught by Savage et al for Ga3+ in view

of Zhou et al., one would achieve a metal chelate which recognizes proteins carrying multiple phosphate groups.

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Savage et al. (US 6,670,159, 12/31/1997) in view of Ehteshami et al. (J. Molecular Recognition 1996; 9: 733-737, of record).

Savage et al. teach, as applied to claims 1-3, 7-8 and 10 above, a chelated metal conjugate comprising a chelator having tridenate chelator function towards multivalent metal ions, wherein said chelate is covalently linked via an amide bond to a molecule having a primary amine group (column 2, lines 24-30). With regards to the chelator, the patent teaches that the chelators include, but are not limited to, nitrilotriacetic acid (abstract). With regards to the molecule, the patent teaches that the molecules include, but are not limited to, enzymes, fluorescent labels, biotin or other detectable moieties (column 2, lines 39-41). With regards to the metal, the patent teaches that the metals include, but are not limited to, the most commonly used metals in metal affinity interactions such as iron or nickel, wherein iron activated chelate conjugates allows for detection of phosphate-containing molecules (column 4, lines 50-52 and column 10, Example XI). Moreover, Savage et al. teach that iminodiacetic acid have been used in metal-ion chromatography for the detection of ferric ions (column 1, lines 33-37). Moreover, Savage et al. teach that it is recognized that in metal-ion chromatography the chelating functionality used to immobilize the metal to construct the chelator metal conjugate is important (column 1, lines 33-35). For example, the patent teaches that iminodiacetic acid has been used with iron due to its tight binding characteristics with ferric ions (column 1, lines, 35-37).

Savage et al. do not explicitly teach that the metal-ion chelate-detectable moiety conjugate further comprises a spacer between the chelator-metal ion and the detectable moiety.

Ehtashami *et al.* disclose a dual heterofunctional soluble polyethylene glycol conjugate comprising a metal chelator, PEG and a detectable moiety, wherein the PEG is between the metal chelator and detectable moiety (Abstract). Specifically, the reference teaches that the presence of the PEG group provides water solubility, but does not affect compounds activity or affinity towards their corresponding conjugate molecules (abstract and page 733, *Introduction*, 1st column, lines 14-15).

It would have been *prima facie* obvious to one of skill in the art at the time the invention was made to combine the teachings of the references so as to incorporate a PEG group between the chelator metal-ion moiety and detectable moiety as taught by Savage et al. in view of Ehtashami et al. One would have been motivated to do so because Ehtashami et al. teach that the presence of the PEG group provides water solubility, but does not affect compounds activity or affinity towards their corresponding conjugate molecules. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by incorporating a PEG group between the chelator metal-ion moiety and detectable moiety as taught by Savage et al. in view of Ehtashami et al, one would achieve a dual heterobifunctional metal-chelate-detectable moiety conjugate which displays greater water solubility and dose not affect the compounds activity or affinity towards their corresponding conjugate molecules.

Claims 36 and 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Savage et al. (US 6,670,159, 12/31/1997) in view of Molecular Probes (MP 21879, Pro-Q™ Oligohistidine Blot Stain Kit #2, 09/27/2001, of record).

Savage et al. teach, as applied to claims 1-3, 7-8 and 10 above, a chelated metal conjugate comprising a chelator having tridenate chelator function towards multivalent metal ions, wherein said chelate is covalently linked via an amide bond to a molecule having a primary amine group (column 2, lines 24-30). With regards to the chelator, the patent teaches that the chelators include, but are not limited to, nitrilotriacetic acid (abstract). With regards to the molecule, the patent teaches that the molecules include, but are not limited to, enzymes, fluorescent labels, biotin or other detectable moieties (column 2, lines 39-41). With regards to the metal, the patent teaches that the metals include, but are not limited to, the most commonly used metals in metal affinity interactions such as iron or nickel, wherein iron activated chelate conjugates allows for detection of phosphate-containing molecules (column 4, lines 50-52 and column 10, Example XI).

Savage et al. does not explicitly teach a kit comprising chelator-metal ion moiety conjugated to a detectable moiety and a secondary reagent for detecting the chelator-metal ion moiety.

Molecular Probes disclose a commercial kit comprising a conjugate of the formula Biotin-X NTA comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the chelator-metal moiety, the reference teaches (page 1, 1st

column, Introduction) that the chelator is nitrilotrioacetic acid and the metal is Ni^{2+}. With regards to the detectable moiety, Molecular Probes teach (page 1, 1st column, Introduction) that the detectable moiety is biotin. The reference further teaches that the kit further comprises a secondary reagent for detecting the conjugate (1st page, 1st column, Introduction, lines 11-14), as well as instructions on how to use the kit. Moreover, Molecular Probes teach that the kit is useful for the detection peptide sequences.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to package the chelated metal conjugate as taught by Savage et al. into a kit useful for the detection of polypeptide or fragment thereof because a kit would insure standardization of reagents for testing. One of ordinary skill in the art at the time the invention was made would have been motivated to make a kit useful for the detection polypeptides or fragment thereof because standard kits enhance the probability of the reproducibility and efficiency of the detection process and further provide for increased marketability, convenience, reliability, and economy.

Claims 1-2, 4 and 7-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Etheshami (1996 "Synthesis and Characterization of Bioaffinity Interactive Heterobifunctional Polyethylene Glycols", Ph.D. dissertation, University of Arizona, of record) in view of Neville et al. (Protein Science 1997; 6: 2436-2445, of record).

Etheshami discloses (page 123, Chapter 5) a heterobifunctional poly (ethylene) glycol derivative having the structure biotin-PEG-IDA and its application in protein purification and characterization using a two phase system. Moreover, the dissertation teaches the effect of IDA in these biochelates for the separation of hemoglobin, a protein with a large number of surface accessible histidines that can interact with the immobilized metal ions and no affinity for biotin (page 126). . With regards to the chelator-metal moiety, the reference teaches (page 89) that the chelator is iminodiacetic acid (IDA) and the metal is Cu2+. The dissertation also teaches (page 83-84) a method of synthesizing the conjugate comprising contacting iminodiacetic acid (IDA) with a molar excess of NHS-biotin under conditions wherein the biotin is transferred to IDA to form the chelator-detectable moiety complex. Etheshami further teaches (page 89) that the synthesis step further comprises mixing the IDA-PEG-Biotin conjugate in a metal ion containing solution,

wherein the conjugate and metal ion are present in an equimolar concentration, i.e. 1:1. The reference further teaches that the conjugates are useful for immobilized metal affinity chromatography (IMAC) (abstract, page 20)

Ehtashami does not explicitly teach the metal ion is Fe^{3+}.

Neville et al. teach that Fe^{3+} loaded IDA metal-ion affinity resin binds acidic and poly-his peptides in addition to phosphopeptides (page 2437, 1st column, 3rd paragraph).

It would have been *prima facie* obvious to one of skill in the art at the time the invention was made to substitute Cu (II) as taught by Etheshami et al. for Fe^{3+} in view of the teachings of Neville et al. One would have been motivated to do so because each of the metal ions have been individually taught in the prior art to be successful at binding poly-his peptides. Thus, one of ordinary skill in the art would have a reasonable expectation that by substituting CU(II) as taught by Etheshami et al. for Fe3+ as taught by Neville et al., , one would achieve a metal chelate which recognizes poly-His peptides such as hemoglobin.

(Note: In order to expedite prosecution, the Examiner will address Applicants arguments pertaining second obviousness rejection (Remarks, Page 5). Specifically, the Examiner will address on the Ehteshami Dissertation because Applicants arguments pertaining to Nieba et al. are not pertinent because the Examiner has withdrawn Nieba et al.).

Applicants respectfully submit that the various moieties found in the affinity reagents disclosed in the Ehteshami Dissertation have different functions than the instantly claimed subject matter. In particular, Applicants submit that as shown in Figure 1.2 of the Ehteshami Dissertation, a chelating matrix coordinating a metal ion bound is bound to a metal support and is also coordinated by a PEG derivative comprising a bioligand. In other words, Applicants assert that the bioligand moiety and not the chelator metal ion moiety that binds to the ligand of interest. In stark contrast, Applicants assert that the chelator-metal ion moiety present in the phosphoprotein detection reagent (PPDR) of claim 1 binds to a phosphorylated amino acid residue in a phosphoprotein. As such, Applicants assert that even if one of ordinary skill in the art were motivated to replace the copper ion in the heterobifunctional polyethylene glycols disclosed in the Ehteshami Dissertation with Ga3+ or Fe3+, the resulting chelator-metal ion links the PEG derivative to the chelating matrix attached to the solid support. Applicants further submit that the

Patents Office assertion, e.g., that the heterobifunctional bispecific chelate polymer has the same function as the instantly claimed PPDRs of claim 1, finds no support in the Ehteshami Dissertation. Notably, Applicants submit that the heterobifunctional bispecific chelate polymers disclosed in the Ehteshami Dissertation bind to proteins by virtue of their bioaffinity ligands. As such, Applicants submit that even assuming arguendo that the heterobifunctional bispecific chelate polymers disclosed in the Ehteshami Dissertation do have the same general functional as the disclosed PPDRs, the individual components of the PPDRs of the presently disclosed subject matter have different structures and functions.

In response to these arguments, the Examiner directs Applicants attention to chapter 5 of the Ehteshami Dissertation beginning on page 125 entitled Application of Heterobifunctional Biospecific Chelate Polymers in Protein Purification and Characterization using Two Phase Systems. Specifically, the Examiner directs Applicants attention to page 126 of the Ehteshami Dissertation which teaches that in order to characterize the pseudo-affinity chelating effect, experiments were performed by charging it, e.g., IDA-PEG-bioligand, with metal ions first and then adding it to the two-phase system, containing the protein, hemoglobin, rich in surface histidine (20 histidines) which has affinity for chelated metal ions, but having no affinity for PAB or biotin. Thus, while the Examiner concedes that Ehteshami Dissertation, as shown in Figure 1.2, that that a bioligand and not the chelator metal ion moiety binds to the ligand of interest, the Examiner recognizes that the Ehteshami Dissertation clearly sets forth a charged metal ion IDA-PEG-bioligand, wherein the chelated metal ion binds to the ligand of interest. Therefore, the moiety taught by Ehteshami Dissertation appears to function as the claimed compound of formula 1 in the sense that chelator-metal ion moiety binds to the ligand of interest. Lastly, the Examiner recognizes that the Ehteshami Dissertation does not explicitly teach the individual components of the instant claimed PPDRs. However, it must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which make up the state of the art with regard to the claimed invention. Furthermore, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what

the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Claims 36 and 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Etheshami (1996 "Synthesis and Characterization of Bioaffinity Interactive Heterobifunctional Polyethylene Glycols", Ph.D. dissertation, University of Arizona, of record) in view of Neville et al. (Protein Science 1997; 6: 2436-2445, of record) in further view of Molecular Probes (MP 21879, Pro-Q™ Oligohistidine Blot Stain Kit #2, 09/27/2001, of record).

Etheshami in view of Neville et al. disclose, as applied to claims 1-2, 4 and 7-14 above, a heterobifunctional poly (ethylene) glycol derivative having the structure biotin-PEG-IDA, wherein IDA has been charged with Fe3+. Moreover, the dissertation teaches the separation of hemoglobin, a protein with a large number of surface accessible histidines that can interact with the immobilized metal ions and no affinity for biotin using the heterobifunctional poly(ethylene) glycol conjugate.

Ehtashami in view of Neville et al. do not explicitly teach a kit comprising a kit comprising chelator-metal ion moiety conjugated to a detectable moiety and a secondary reagent for detecting the chelator-metal ion moiety.

Molecular Probes disclose a commercial kit comprising a conjugate of the formula Biotin-X NTA comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the chelator-metal moiety, the reference teaches (page 1, 1st column, Introduction) that the chelator is nitrilotrioacetic acid and the metal is Ni^{2+}. With regards to the detectable moiety, Molecular Probes teach (page 1, 1st column, Introduction) that the detectable moiety is biotin. The reference further teaches that the kit further comprises a secondary reagent for detecting the conjugate (1st page, 1st column, Introduction, lines 11-14), as well as instructions on how to use the kit. Moreover, Molecular Probes teach that the kit is useful for the detection peptide sequences.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to package the chelated metal conjugate as taught by Etheshami et al. in view of Neville et al. into a kit useful for the detection of polypeptide or fragment thereof because a kit would insure standardization of reagents for testing. One of ordinary skill in the art at the time

the invention was made would have been motivated to make a kit useful for the detection polypeptides or fragment thereof because standard kits enhance the probability of the reproducibility and efficiency of the detection process and further provide for increased marketability, convenience, reliability, and economy.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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